Universidade de Lisboa

Faculdade de Farmácia

Novel shape in scored orodispersible tablets applying Design of Experiments

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Mestrado Integrado em Ciências Farmacêuticas

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Monografia de Mestrado Integrado em Ciências Farmacêuticas apresentada à Universidade de Lisboa através da Faculdade de Farmácia com colaboração da Università Degli Studi di Milano

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Abstract

Drug Delivery Systems (DDS) are a strategic tool that has become increasingly sophisticated over the years. Their main contributions involve expanding the life cycle of pharmaceutical products, by improving the administration process according to the patient's needs. Since the drug delivery through oral route still represents the most common and preferred way of drug administration, our work of study relies on the development of orodispersible tablets (ODTs). This dosage form provides a quick onset of action and therefore was chosen as an alternative for paediatric, geriatric and mentally ill patients were the swallowing ability may be compromised.

In the present study orodispersible tablets with a new shape were produced by direct compression using furosemide as the model drug. The production with this novel punch design led to scored tablets with a cloverleaf shape, thus allowing dose flexibility. The tablets were evaluated by thickness and diameter, uniformity of weight and of content, uniformity of the tablet's subunits, resistance to crushing, weight loss, wetting time, water absorption ratio and disintegration time. Through Design of Experiments (DoE) was done a 2^2x3^1 full-factorial test that showed the influence of three independent variables (upper punch compression force, tablet weight and speed of rotation of tabletting machine) on the tablet's properties.

The obtained ODTs were according to the limits for both weight and content uniformity and revealed tablet units with very low coefficients of variation and satisfactory mean percentages of furosemide. The results for resistance to crushing revealed very high values corroborated by low friability of tablets. They also showed uniformity of the subdivided tablets with very low mass deviations and minimum percentage of mass lost during breaking process. The biopharmaceutical tests revealed a different outcome of what was expected from this dosage form. All the disintegration and wetting times failed to comply with the required standards along with the water absorption ratio, thus showing space for improvement.

Keywords: Cloverleaf punch; Design of Experiments; Direct compression; Orally disintegrating tablet; Divisible.

Resumo

Os sistemas de administração de fármacos têm, ao logo do tempo, logrado obter um acentuado grau de desenvolvimento com o objetivo de ultrapassar as limitações terapêuticas existentes. Como principal objetivo é visada a expansão do ciclo de vida dos produtos farmacêuticos, bem como melhorar o processo de administração dos mesmos de acordo com as necessidades da população alvo. Uma vez que a via oral representa o modo de administração mais comum e utilizado, o presente trabalho tem como objeto de estudo o desenvolvimento de comprimidos orodispersíveis (ODTs). Esta forma farmacêutica proporciona um início de ação rápido e apresenta como aspeto diferenciador o seu possível uso em pacientes pediátricos, geriátricos e mentais, onde a capacidade de deglutição pode estar comprometida.

No presente estudo, os comprimidos orodispersíveis com furosemida como fármaco-modelo foram produzidos por compressão direta e apresentavam uma forma inovadora. Na produção recorreu-se ao uso de punções em forma de trevo de quatro folhas, originando comprimidos divisíveis em quatro, permitindo assim possíveis ajustes de dose. Os comprimidos foram posteriormente avaliados em termos de espessura e diâmetro, uniformidade de teor e massa, uniformidade da divisão em quatro partes do comprimido, resistência ao esmagamento, friabilidade, tempo de molhamento, quantidade de água absorvida e tempo desintegração. Através do desenho experimental, fatorial (2^2x3^1), foi possível avaliar a influência de três variáveis independentes (força de compressão do punção superior, massa do comprimido e velocidade de rotação da máquina de comprimidos) nas propriedades dos comprimidos produzidos.

Os comprimidos obtidos encontravam-se de acordo com os limites estabelecidos de uniformidade de teor e massa e, após divisão, apresentaram subunidades com coeficientes de variação muito baixos e com percentagens de furosemida satisfatórias. Os resultados de resistência ao esmagamento revelaram valores muito elevados corroborados pela baixa friabilidade de comprimidos. Constatou-se ainda a uniformidade de massa nas subdivisões dos comprimidos, com desvios muito baixos e percentagens mínimas de perda de massa durante o processo de quebra. Os testes biofarmacêuticos revelaram um resultado diferente do esperado para esta forma farmacêutica. Os tempos de desintegração e molhamento não cumpriram com os padrões exigidos, bem como o índice de absorção de água que se revelou baixo, o que induz ainda existir espaço para melhoria.

Palavras-chave: Punções em forma de trevo de quatro folhas; Desenho experimental; Compressão direta; Comprimidos orodispersíveis; Divisível.

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Acronyms and Abbreviations

API	Active Pharmaceutical Ingredient
CCS	Croscarmellose Sodium
Coef	Coefficient
DDS	Drug Delivery Systems
DoE	Design of Experiments
EBT	Easy Breakable Tablet
GIT	Gastro-Intestinal tract
L-HPC	Low-substituted hydroxypropylcellulose LH-11
MCC	Microcrystalline cellulose
min	Minutes
mL	Millilitre
mm	Millimeter
µm	Micrometer
M	Molar
nm	Nanometer
ODT	Orodispersible Tablet
p	p-value
RH	Relative Humidity
rpm	Rotations per minute
s	Second
S	Speed of rotation of the tablet press
SSG	Sodium Starch Glycolate
UF	Upper punch compression force
W	Weight of tablets

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1 Introduction

Drug Delivery Systems (DDS) are a strategic tool that has become increasingly sophisticated over the years. Their main contributions involve expanding the life cycle of pharmaceutical products, by improving the administration process according to the patient's needs. As the pharmaceutical departments evolve and acquire a better knowledge on how the physicochemical and biochemical parameters of the products are influenced, new and enhanced drug delivery strategies are developed (1).

For most therapeutic agents used to produce systemic effects, drug delivery through oral route still represents the most common and preferred way of drug administration both for solid and liquid dosage forms. The preference is justified by their several benefits including ease of administration, accurate dosage, self-medication, versatility and most importantly, patient compliance. Tablets, when compared to liquid dosage forms, have advantages related to chemical and physical stability, ease of packing and accurate dosing during the preparation procedure. They are also convenient to handle and can be mass-produced, with robust and controlled production procedures resulting in an attractive form with very good quality-price relation (2). For this reasons, they stand as the most popular solid dosage form although, not entirely suitable for specific populations with a particular focus on paediatric, geriatric and mentally ill patients (3–5). The human physiology of the gastrointestinal tract (GIT) is associated with intrinsic limitations, which is why water is a prerequisite in gulping this solid dosage forms. Also, patients with bronchitis, allergenic cough, cold, bedridden, difficulty in chewing or suffering dysphagia (difficulty in swallowing), tremors problems and unconscious have trouble in gulping the tablets without drinking water (6). Besides the enumerated situations, where may exist physical discomfort, there is also the possibility of psychological distress resultant from previous bad experiences, like tablet sticking or scratching the oesophagus. During the recent years, damage of oesophagus by retention of tablets has been reported. Beyond causing discomfort and pain, the mucous membrane may be irritated and the underlying tissue damaged. Most common is a regular cauterisation, but also drugs that intumesce with moisture in the oesophagus can cause severe damage (7). Another target population is represented by patients with persistent nausea, who are travelling, or who have little or no access to water (5). To avoid noncompliance and ineffective therapies from the stated populations, researchers developed an innovative drug delivery system moulded in the late 80s and brung in to the market in early 90s. The new form can be designated as Orodispersible tablets (ODTs), Orally disintegrating tablets, Quick disintegrating tablets, Fast disintegrating tablets, Rapid

dissolving tablets, Fast dissolving tablets, Mouth dissolving tablets, Porous tablets and Rapid melts (6). Thus, orodispersible tablets are solid single-unit dosage forms like conventional tablets but composed of super disintegrants, which help them to dissolve quickly in the oral cavity in the presence of saliva, without the need for water or any difficulty of swallowing and chewing (1).

Recently, the European Pharmacopoeia has used the term orodispersible tablets and described them as “uncoated tablets intended to be placed in the mouth where they disperse rapidly, within 3 min before being swallowed” (8). The United States Pharmacopoeia has also approved the previously stated designations of dosage forms as orodispersible tablets. On the other hand, the Food and Drug Administration of United States defined ODTs as: “A solid dosage form containing a medicinal substance or active ingredient which disintegrates rapidly usually within a second when placed upon the tongue” (9). A significant difference in the ranges of disintegration times is noted. Nevertheless, the highlight relies on the need for the lowest disintegration times possible, to fulfil the patient’s expectations and lead to an effective therapy.

Besides the main satisfactory reasons presented for this dosage form, they also provide a quick onset of action since, when placed in the mouth, disintegrate instantly facilitating the drug release and dissolution in the saliva. After that, drugs can be absorbed from mouth, pharynx, oesophagus or other sections of the GIT as the saliva passes down into the stomach. In such cases, the bioavailability of the drug and safety are significantly greater than those observed from the conventional tablet dosage form (1,2,4,10). This can be justified by the minimisation of the hepatic metabolism’s first passage effect, due to pre-gastric absorption through the highly vascular mucosal lining of the mouth. Here, the drugs move through the sublingual or buccal capillaries and veins to the jugular vein and superior vena cava directly into heart and circulation arteries. This route is more efficient because avoiding the first passing through the liver, where an extensive hepatic detoxification takes place, it is possible to decrease the dosage needed in the formulation (11).

Although this dosage form stands as a very promising solution, it also has limitations that need to be addressed. Some specifics that need to be taken in consideration are the tablet’s hygroscopic nature that demands to be kept in a dry place with special packaging for proper stabilisation and safety. Some of the manufacturing techniques and packaging may be costly (e.g. lyophilisation). Also, ODTs usually have inadequate mechanical strength and so must be handled carefully. The active pharmaceutical ingredients (APIs) may have a limited dose in some manufacturing techniques, and if badly formulated, the tablet may possess and leave an obnoxious feel and grittiness in the oral cavity. The patients prescribed with

anticholinergic medicine, with Sjogren's syndrome or dryness of the mouth with lessening saliva production may not be preeminent contenders for ODTs (4,5,11).

Taking into consideration all the ODTs potentialities and limitations urges the need to maximise their desirable characteristics and minimise possible problems. Aiming for the ideal tablet the properties highlighted are their oral administration without the need for water, yet disintegrating and dissolving in saliva within seconds, along with the ability to permeate the oral mucosal tissue. They should be free from bitter taste or embraced with pleasant mouthfeel, alongside with good taste masking properties. It's important that they present sufficient strength to withstand the rigours of the manufacturing process and post-manufacturing handling, with minimal sensitivity to environmental conditions (temperature and humidity). Other relevant features are the ability to diffuse and partition into the epithelium of the upper GIT (log P >1); to be partially non-ionized at the oral cavity's pH; leave minimal or no residue in mouth after administration and must be cost-effective enough (6).

Before selecting the proper manufacturing approach to produce ODTs, is extremely important to address all the factors that stand as a challenge in the formulation. The aspects to consider are palatability, mouthfeel, grittiness, after-effect, mechanical strength, size, hygroscopicity, amount of drug and aqueous solubility. As most drugs are unpalatable, ODTs usually contain the API in a taste-masked form to leave a soothing or cooling sensation. Particles should be less than 50 μm to avoid grittiness, and the overall tablet's size should be larger than 8mm to be easily handled. Since many forms are hygroscopic and cannot maintain physical integrity, is necessary to develop specialised protective packaging. The application of technologies used for ODTs is limited by the amount of drug that can be incorporated into each unit dose. For lyophilised dosage forms, the drug dose must be lower than 400 mg for insoluble drugs and less than 60 mg for soluble drugs (11,12).

The performance of ODTs depends on the technology used in their manufacture. Their orally disintegrating property is attributed to the quick ingress of water into the tablet matrix, which creates porous structure and results in rapid disintegration. Hence, the primary approaches to develop ODTs include maximising the porous structure of the tablet matrix, incorporating the appropriate disintegrating agent and using highly water-soluble excipients in the formulation (1). It is clear that ODT excipient mixtures play a significant role in the success of these formulations and when chosen wrongly, can lead to compromised stability of the API and reduced shelf life of the final product (13).

Along with other classes of pharmaceutical excipients, lubricating agents are added to the formulation of solid dosage forms to aid in the manufacturing process and

ensure appropriate quality of the finished products. The lubricant is best identified as a suitable material, in a small amount that when interposed between two rubbing surfaces, reduces friction arising at the interface. The choice of a type and amount of lubricant is influenced by the deformation behaviour of the major component of the blend. Also, the choice of a suitable binder for a tablet formulation requires extensive knowledge of binder properties for enhancing the strength of the tablet and the interactions between the various constituents of a tablet. Addition of a binder, which increases elasticity, can decrease tablet strength because of the breakage of bonds as the compaction pressure is released. Achievement of desired dissolution rate of drug substances from a tablet requires overcoming the cohesive strength and breaking into primary particles. This can be achieved by adding proper disintegrants in the adequate fractions into the formulations (14,15).

There are several methods for the preparation of ODTs, but the prepared products vary in their properties depending on the method chosen. The properties in which they vary are the tablet's mechanical strength, swallowability, bioavailability, drug dissolution in saliva, stability, and to some extent taste (2). The various process of manufacturing of orodispersible tablets are Freeze-Drying or Lyophilization, Tablet Molding, Spray Drying, Mass-Extrusion, Cotton Candy Process, Compression, Melt Granulation, Phase Transition, Sublimation, Wet/Dry Granulation and Direct Compression. (11)

Among the above technologies, direct compression is the most convenient and cheap way to produce tablets with sufficient structural integrity. It is the most preferred because of its simplicity, rapidity, economic reasons and stability concerns (10,11). The tablets prepared by direct compression disintegrate into API particles instead of granules, that come into direct contact with the dissolution fluid and exhibit comparatively faster dissolutions. The high compaction pressure involved in the production of tablets by slugging or roller compaction can be avoided by adopting direct compression. The chances of wear and tear of punches and dies are less when compared with the other techniques. Also, materials are "in process" for a shorter period of time and in the absence of water, resulting in less probability of contamination or cross-contamination, and making easier to meet the requirement of current good manufacturing practices. Due to fewer unit operations, the validation and documentation requirements are reduced (16).

Pharmacists are in the ideal position to become familiar with the various technologies and educate their patients on what to expect upon taking their first dose. The majority of patients receiving ODT formulations have little understanding of this new dosage form and may be surprised when tablets begin to dissolve in the oral

cavity. They also might expect a faster onset of therapeutic action, and therefore clarification from the pharmacist is essential to avoid any confusion or misunderstanding (11).

About 92% of the ODT world market is divided into three therapeutic categories but still has a lot to grow based on the existent amount of drug candidates (Figure 1):

1. Central nervous system (50% market share) with the highest potential for success with ODTs are treatments for gastroesophageal reflux disease, pain, schizophrenia and other CNS diseases, Parkinson's disease, migraine, nausea and sleep nervous system;
2. Gastrointestinal (29%), and
3. Oncology (13%).

S No.	Category	Examples
1	Antiprotozoal drugs	Metronidazole, tinidazole, omidazole, benznidazole, clioquinol, decoquinate etc.
2	Antihistaminic drugs	Methapyrilene, Chorphnaramine, Buclizine, Methadiazine, loratadine, cinnarizine,, Diphenhydramine HCl,Astemizole, Acrivastine, cetrizine, fexofenadine, triprolidine, etc.
3	Anthelmintic drugs	Levamisole, Metrifonate, Piperazine citrate, Diethyl carbmazine, Albendazole, Mebendazole, thiabendazole, Oxamniquine, livermectin,praziquantel, Pyrantel pamoate
4	Gastro intestinal drugs	Granisetrone, Nizatidine, Cimetidine, Lansoprazole, Rabeprazole, Ranitidine, Famotidine, Omeprazole, Pantoprazole, Roxatidine, Esomeprazole
5	Anti arrhythmic drugs	Mexiletine, Tocainide, Phenytoin, Quinidine sulphate, Disopyramide, Flecainide
6	Antihypertensive drugs	Telmisartan, Hydrochlorthiazide, Felodipine, Nifedipine, Prazocin HCl, Nicardipine, Diltiazam, Verapamil, Amlodipine, Losartan
7	Diuretics	Furosemide, Bumetanide, Dichlorphenamide, Spironolactone, Amiloride, Triameterene, Chlorthalidone, Chlorthiazide, Acetazolamide
8	Antibacterial agents	Cefexime, Cefpodoxime, Azithromycin, Ciprofloxacin, Nalidixic acid, Rifampicin, Erythromycin, Tetracycline, Ampicillin, Amoxycillin
9	Antidepressant	Fluoxetine, Sertaline, Mianserin HCl, Trazodone HCl, Trimipramine Maleate, Nortryptiline
10	Antidiabetic drugs	Voglibose, Metformin, Pioglitazone, Glipizide, Tolbutamide, Glibenclamide, Chlorpropamide
11	NSAIDS	Aceclophenac, Fenclofenac, Ibuprofen, Diclofenac Sodium, Mefenamic acid, Naproxen, Celecoxib
12	Corticosteroids	Prednisolone, beclomethasone, Betamethasone,
13	Anxiolytics, Sedative and Hypnotics	Amylobarbitone, Alprazolam, Diazepam, Lorazepam, Nitrazepam

Figure 1 Drug Candidates for ODTs *Retrieved from* (6)

In Portugal, there are several ODTs commercialized with special focus on the group of drugs that act in the Central Nervous System (CNS) that represent the majority. (Figure 2)

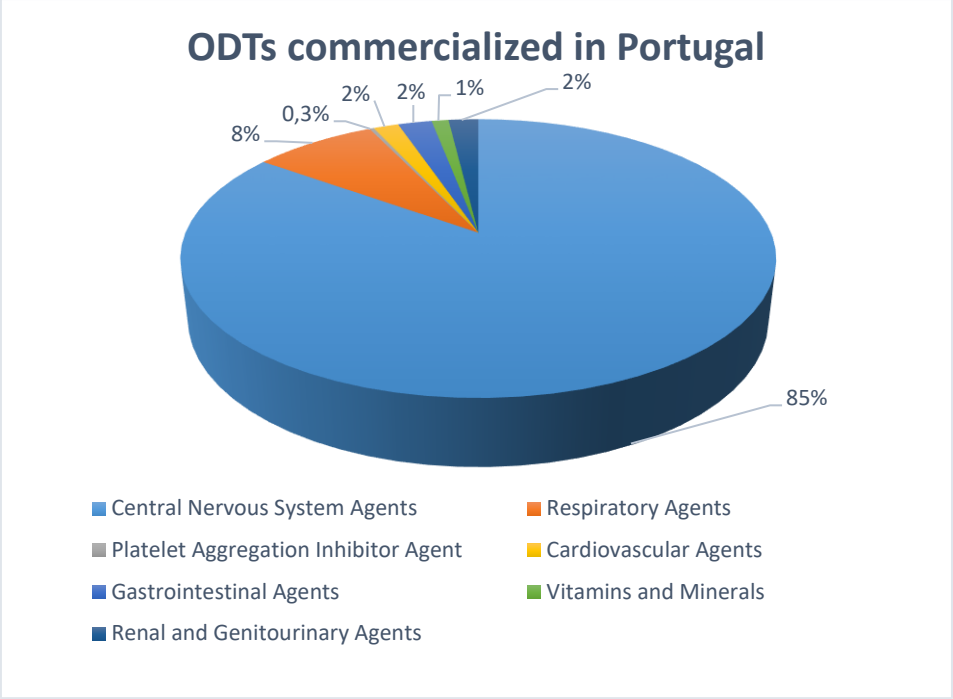

Figure 2 ODTs commercialized in Portugal organized according their category. Adapted from (17)

A key reason that makes companies choose an ODT over other delivery technologies is that the first is relatively easy and often less risky delivery option to develop. Since the route of administration remains the same, ODTs that are formulated as bioequivalent line extensions or generic versions of an existing oral dosage form have minimal clinical requirements to gain approval. Using ODT technology to extend the patent life and market exclusivity of an established drug boosts the value of a brand, fending off generic erosion and thereby increasing revenues (11). Also, recent market studies indicate that more than half of the patient population prefers ODTs to other dosage forms and most consumers would ask their doctors for ODTs (70%), purchase ODTs (70%), or prefer ODTs to regular tablets or liquids (>80%) (18).

However, the constant search for novel characteristics that add more value to the existing products led to the appearance of scores line in ODTs, as studied in the present work. Tablets may bear a break-mark or break-marks and may be subdivided into parts, either to ease the intake of the medicinal product or to comply with the posology. The most important advantage of score lines is that they provide for dose flexibility: the patient can easily adjust the dose in response to medication effects or to comply with the labelled dosage and administration instructions. Dose flexibility can be especially crucial for medications that show strongly patient-dependant effect levels or have a narrow therapeutic index, such as warfarin or levothyroxine (19). Many manufacturers charge the same or similar prices for different strengths of tablets of the

same medication, and hence it is possible to purchase high-strength tablets, split them and use them as relatively cheap low-strength tablets, this has led many healthcare plans to establish mandatory tablet splitting policies (20). However, many patients are confronted with scored tablets that are broken unequally and with difficulty, reducing compliance and reliance on the medication (21,22). Tablets frequently break in uneven parts and loss of product can occur due to crumbling and powdering. Health characteristics, such as the presence of peripheral neuropathy, decreased grip strength and manual dexterity, can affect a patient's ability to break tablets. As these impairments are associated with ageing and age-related diseases, such as Parkinson's disease and arthritis, difficulties with breaking tablets could be more prevalent in this populations (23). Possibilities to reduce splitting difficulties are breaking instructions, tablet-splitters and breaking in advance. The factors influencing the performance of score lines are shape, size, curvature and thickness of the tablet and the form and deepness of the score line. Their performance can be evaluated through the breaking ease, uniformity of mass of subdivided units and loss of mass during breakage (19).

In this study, direct compression was chosen given the ease of manufacture, low cost comparing to other procedures, and the ease of which score lines can be incorporated. Following the addition of superdisintegrants in the correct fraction, ODTs with the desired properties can be formulated using direct compression (2). The chosen API was Furosemide, a potent loop diuretic used in the treatment of oedematous states associated with congestive heart failure, cirrhosis of the liver, renal disease and chronic hypertension. The usual oral doses of furosemide are 20, 40 and 80 mg given as a single dose to suit the age of the patient, the condition and when there is an improvement or a decline in symptoms. For such reasons, a split tablet formulation would provide flexibility of dosing while notably reducing the cost of providing multiple doses. According to the Biopharmaceutics Classification System (BCS) furosemide is a Class IV compound with low solubility and low permeability. Because of its weak acidic properties (pKa=3.8), furosemide is mostly absorbed in the stomach and upper intestine, but also from the oral mucosa following sublingual administration. Bioavailability of furosemide is about 37-70%, and the peak plasma concentration is reached within 60 to 90 min. Due to the properties mentioned, it is beneficial to formulate furosemide as a scored ODT, in an attempt to increase the onset of action through rapid disintegration and dissolution. To our knowledge, no furosemide containing ODTs are commercially available. Therefore, the purpose of this study was to develop and produce by direct compression a furosemide cloverleaf shaped ODT with a cross line (Figure 3), and investigate the impact of the upper punch

compression force, tablet weight and speed of rotation of the tablet press on the properties of the obtained tablets. The results were based on quality control tests on the OTs such as diameter and thickness, weight and content uniformity, variation of the subdivided units and weight loss upon breakage, resistance to crushing, friability, wetting time, water absorption and disintegration time (24). In the statistical analysis Design of Experiments (DoE) was used. DoE is a system that conducts a series of predetermined changes in the independent variables, allowing the quantification of the linear and quadratic effects alone, and the linear effects in combination with one another. The traditional method of formulation optimisation relies on a univariate or one variable at a time approach, from which we cannot generate mathematical equations to demonstrate the variation in responses as a function of the defined factors, as is possible in DoE (25).

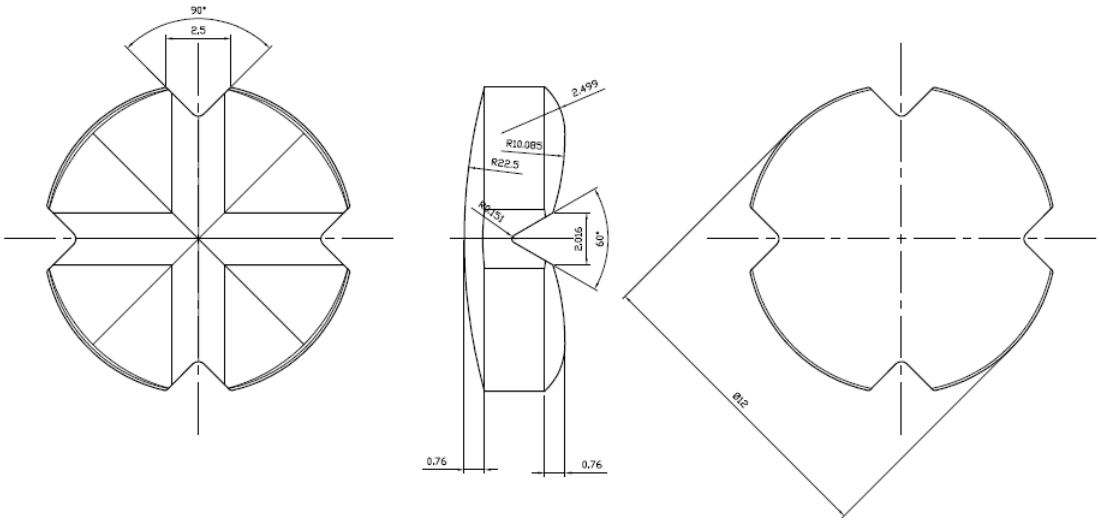

Figure 3 Diagrammatic representation of orally dispersible tablets produced using "Easy Breakable Tablet" punch novel design

2 Objectives

- Formulate, evaluate and optimise the viability of scored orodispersible tablets of Furosemide with a cloverleaf shape;

- Production of orodispersible tablets by direct compression varying three relevant parameters (compression force, weight and tabletting machine speed);

- Analyse and evaluate the influence of each variable parameter on the produced tablets through Design of Experiments;

- Compare the tablets produced in this study with previous scored tablets produced in the same conditions but with the classic geometry.

3 Materials and Methods

3.1 Materials

Furosemide, chosen as the model drug for the formulation, was obtained from Tekofarma (Turin, Italy). Prosolv ODT G2®, a co-processed excipient, was acquired from JRS Pharma (New York, USA) and contains a mixture of microcrystalline cellulose (MCC), colloidal silicon dioxide, mannitol, fructose and crospovidone. Magnesium stearate, used as a lubricant purchased from Carlo Erba Reagents (Milan, Italy) and the colloidal silica dioxide (Aerosil 200) obtained from Evonik Industries (Rheinfelden, Germany). Methylene blue was acquired from Carlo Erba Reagents (Milan, Italy) to measure the wetting time, and finally, NaOH was purchased from A.C.E.F. (Fiorenzuola d'Arda, Italy) to perform the uniformity of content test.

3.2 Methods

3.2.1 Preparation of tablets

For the preparation of the orodispersible tablets, furosemide (15% w/w) alongside with a selection of tailored excipients were used. The latter choice was Prosolv ODT G2® a second generation co-processed ready-to-use excipient. This term designates a matrix composed of two or more interacting excipients at a subparticle level. This choice was made based on previous studies that revealed an improved functionality with substantial benefits of the incorporated excipients and minimisation of their drawbacks (16,26,27).

Prosolv ODT G2®, used at 82.25% (w/w), is the unique combination of soluble and insoluble excipients, manufactured using co-processing technology. This excipient matrix is based on microcrystalline cellulose, colloidal silicon dioxide, mannitol, fructose and crospovidone, and designed specifically for orally disintegrating tablet formulations. This powder matrix aims to address manufacturing and formulation challenges, by presenting an outstanding flowability, leading to increased productivity, and enhanced compressibility, without requiring additional binders or disintegrants. Along with other co-processed mannitol based excipients, Prosolv ODT G2® increases

the patient compliance by its pleasant, smooth and creamy mouthfeel and fast disintegration in the oral cavity, without the need for water (15,28).

For the preparation of ODTs with ready-to-use excipients, the addition of a lubricant was mandatory. Therefore, magnesium stearate (1.5% w/w) was used in the formulation (29,30). Finally, to improve the flowability of the powder hence optimising the direct compression process, colloidal silicon dioxide (1.25% w/w) was added as a glidant (30,31).

Each substance was weighed using a magnetic compensation analytical balance (Crystal 500, Gibertini, Italy). Furosemide, Prosolv ODT G2®, and colloidal silicon dioxide were initially mixed manually in a polyethylene bag for 10 min, before the addition of magnesium stearate (32). Then, all excipients were appropriately mixed for 2 min, by the same operator each time.

Finally, 12 batches of orodispersible tablets were produced by direct compression using a rotary tablet press (AM8S, Officine Ronchi, Milan, Italy) with a novel easy breakable tablet (EBT) punch design (B&D Italia, Italy). This new EBT presented a cloverleaf shape (Figure 3), with an upper side with a unique cross break line and a lower concave side. During the production phase, three independent variables were changed: the upper punch compression force, tablet weight and speed of rotation of the tablet press.

The tabletting process, as well as afterwards storage of the ODTs, took place in a conditioned room at 21°C and 45% of RH.

3.2.2 Physical characterisation of tablets

The tablets were evaluated for uniformity of mass, thickness, mechanical strength, resistance to crushing and content uniformity of furosemide. Where applicable, tests were carried out according to the European Pharmacopeia requirements for ODTs stated in the 8th edition, and more recently the standards for scored tablets (8,33).

3.2.2.1 Thickness and Diameter

Ten tablets were randomly selected from each batch and tested for the mean and standard deviation of thickness and diameter using a Mitutoyo digimatic caliper ID-C112EXB (Andover, UK).

3.2.2.2 Uniformity of mass

The weight variation of the whole tablets was tested according with the Section 2.9.5 Uniformity of mass of single-dose preparations of the European Pharmacopeia (8), where twenty tablets were randomly selected, weighted (Crystal 500, Gibertini, Italy) and the average mass, standard deviation and coefficient of variation were determined.

3.2.2.3 Uniformity of mass of the subdivided tablet

The uniformity of mass of subdivided tablets was done and evaluated according to the Monographs on dosage forms of the European Pharmacopoeia (8). Thirty tablets were randomly selected and broken by applying force on the centre of the score line with the thumb. Tablet splitting was carried out by a single operator to avoid any influence in the results caused by the splitting technique. This method of breaking was repeated in the following tests when required. This procedure was chosen based on preceding articles that elected it as more convenient and loss of mass minimiser (34). From all the four parts obtained from one tablet, only one was selected for the test, and the others rejected. Then the thirty parts were weighed individually (Crystal 500, Gibertini, Italy) and the average mass, standard deviation and coefficient of variation were calculated.

3.2.2.4 Uniformity of content

One tablet from each batch was weighed separately, broken into four segments by applying force to the centre of the tablet with the thumb, and each segment was weighed. Glass beakers (600 mL) were filled with 200 mL 0.25 M NaOH solution, and each of the 4 tablet segments were placed in each beaker and were subject to magnetic agitation (MIX 15 eco, 2mag, Muenchen, Germany). The test was carried out for 30 min, to ensure complete dispersion of furosemide, and the beakers were rotated 90° every 2 min to guarantee that the magnetic stirrers covered the entirety of the beaker. The samples were collected by a peristaltic pump (IPC Ismatec, Wertheim, Germany) and analysed by spectrophotometric analysis (Lambda 35, Waltham, USA Italy) at 271 nm wavelength using a quartz cuvette of light path 1 mm (SUPRASIL type 170-QS, Hellma, Milan, Italy). The calibration curve from which the furosemide content

was determined, equation 1, was obtained with different dilutions (1:2, 1:4, 1:5, 1:10) of a stock solution (0.160 mg/mL) of furosemide.

$$Abs = 5.8476\,[Fur] - 0.0007 \quad (1)$$
$$R^2 = 0.99998$$

Where Abs represents the UV absorbance at 271 nm and [Fur] the concentration of furosemide in mg/mL.

3.2.2.5 Weight Loss

Ten tablets were collected arbitrarily from each batch, and their weight was recorded. (Crystal 500, Gibertini, Italy) Then, each tablet was placed on a solid straight surface with the score line up and, broke into four pieces by applying force with the thumb. The pieces were weighed separately, and together, and the percentage of weight loss was calculated and afterwards evaluated by the content uniformity of each tablet segment.

$$(\%)Weight\ Loss = \frac{wt - w\sum 4p}{wt} \times 100 \quad (2)$$

Where, wt represents the tablet weight before fracture and wΣ4p, the weight summation of each of the four pieces.

3.2.2.6 Resistance to crushing

This test intends to determine the tablet's resistance to crushing in Newton (N), under defined conditions, thus mimetizing the necessary force made by patients to break the tablet. The measurement of the resistance to crushing was carried out (Erweka TBH-28, Heusenstamm, Germany) by the operating procedure listed in section 2.9.8 Resistance to crushing of tablets of the European Pharmacopoeia. The tablets were placed between the jaws of the apparatus, taking into account, the cloverleaf shape and break-mark (Figure 3), orientating the tablets in each batch the same way. The resistance to crushing was measured by placing the tablet flat, with the score line facing the direction of the force application (8).

3.2.2.7 Friability

To determine the ability of the tablets to withstand abrasion, friability tests were performed, and the forces they are subjected to, during packaging, handling, and shipping, were mimicked (35). Friability tests were carried out according to section 2.9.7 Friability of uncoated tablets of the European Pharmacopeia, for tablets with a unit mass equal to or less than 650 mg (8). A sample of whole tablets corresponding as near as possible to 6.5 g was taken from each batch. The tablets are carefully dedusted before testing. The weight was recorded and the tablets placed in the drum (TA3, Erweka, Heusenstamm Germany) and rotated at 25 rpm for 4 min, equalling to 100 rotations. Tablets were subsequently cleaned with a brush, to remove any loose dust from the surface and then, reweighed to establish the weight loss and calculate the friability percentage.

$$(\%)Friability = \frac{wi-wf}{wf} \times 100 \quad (3)$$

Where wi represents the initial weight before the test and wf the final weight after the test.

3.2.3 Biopharmaceutical characterisation of tablets

The tablets were evaluated for wetting time, water absorption ratio and disintegration time. Where applicable, tests were carried out according to the European Pharmacopeia requirements for ODTs stated in the 8th edition and other published articles.

3.2.3.1 Wetting time

To evaluate the wetting time, an 11.5 cm diameter Petri dish, with a 10 cm diameter circular piece of tissue paper placed inside, was filled with 15 g of distilled water. Afterwards, three tablets from each batch were tested separately. First, a small quantity of methylene blue was applied to the centre of the tablet's curved surface with a spatula, and then the tablets were placed with the score line down on the surface of the tissue paper. This test is based on the time required for the distilled water to reach the upper surface of the tablet thus inducing the transition of methylene blue from powder to solution. The time was recorded, and the mean value used to determine the overall wetting time (36).

3.2.3.2 Water absorption ratio

Analogous to the previous method, a Petri dish with a diameter of 11.5 cm and a circular piece of tissue paper with a diameter of 10 cm were used, though this time the dish was filled with 25 g of distilled water. Three tablets from each batch were individually weighed and tested by placing on the tissue paper, this time with the score line up. Then, when the water had risen through the tablet to wet the surface completely, the wet tablet was removed from the paper with a spatula and reweighed. The water absorption ratio was determined according with equation 4, and the mean of the three tablets was recorded.

$$(\%)Water\ absorption\ ratio = \frac{wf - wi}{wf} \times 100 \quad (4)$$

Where, wf is the tablet weight after absorption of the water, and wi indicates the initial tablet weight (36).

3.2.3.3 Disintegration

Disintegration testing was performed as described in section 2.9.1 Disintegration of tablets and capsules of the European Pharmacopoeia, where three tablets from each batch were tested using a 3-position disintegration apparatus (DT3 Sotax, Allschwil Switzerland). Each of the three baskets were placed in 800 mL distilled water at 37°C ± 2°C, and the time required for three tablets to complete disintegration was recorded. For the purposes of this test complete disintegration is defined as the state in which anything remains on the lower surface of the discs and if it does, should be just a soft mass having no tangible firm core (8).

3.2.4 Experimental design and validation

3.2.4.1 Design of Experiments

A 2^2x3^1 full-factorial was the experimental design of choice for the study, with two factors with two levels and one factor with three levels. It was employed to design an experimental matrix (Table 1), that simultaneously studies the effect of three independent variables on the properties of the produced tablets. The three independent variables assessed in this study were: upper punch compression force (UF), weight of tablets (W), and speed of rotation of the tablet press (S). Starting with the compression force, the range of values, for each independent variable, was set based on previous studies and in what was deemed acceptable for the production of ODTs. A UF of 13.5 kN seemed appropriate considering the punch and dial diameter and the mechanical strength required, and so based on a 20% variation of this value, 10.8 kN and 16.2 kN were chosen as suitable minimum and maximum values. The weight of tablets selected for this study was 400 mg and 500 mg. Lastly, the speed of rotation set was 10 rpm and 20 rpm, according to the minimum and maximum values allowed by the tabletting machine.

If for each independent variable there were three correspondent levels as seen in Table 1. For better interaction-effects evidence and improved prediction of process behaviour, 27 experiments would have to be done (3^3 full factorial design) however, given constraints on resources, the 2^2x3^1 full-factorial was used to reduce the number of trials to 12, but still giving accurate and reproducible results.

Table 1 Design of experiments matrix.

Batch	***Coded Levels***			***Levels***
	UF	W	S	
1	-1	-1	-1	10.8 kN – 400 mg – 10 rpm
2	0	-1	-1	13.5 kN – 400 mg – 10 rpm
3	1	-1	-1	16.2 kN – 400 mg – 10 rpm
4	-1	1	-1	10.8 kN – 500 mg – 10 rpm
5	0	1	-1	13.5 kN – 500 mg – 10 rpm
6	1	1	-1	16.2 kN – 500 mg – 10 rpm
7	-1	-1	1	10.8 kN – 400 mg – 20 rpm
8	0	-1	1	13.5 kN – 400 mg – 20 rpm
9	1	-1	1	16.2 kN – 400 mg – 20 rpm
10	-1	1	1	10.8 kN – 500 mg – 20 rpm
11	0	1	1	13.5 kN – 500 mg – 20 rpm
12	1	1	1	16.2 kN – 500 mg – 20 rpm

3.2.5 Statistical Analysis

Results obtained from the experiments were expressed as a mean, standard deviation and coefficient of variation using Microsoft Excel software (Redmond, WA, USA). Statistical experimental design, evaluation of the model's quality of fit and analysis of the data, including calculation of the constants and regression coefficients was conducted using the STATISTICA 7 (Statsoft, USA) statistical software.

4 Results and Discussion

4.1 Characterisation and statistical analysis of tablet batches

The results of the 12 batches (Table 2) reflect the effects of each independent variable (compression force, weight and speed) on the production of the scored ODTs.

4.1.1 Visual aspect of the tablets

The necessity of being able to provide a unique identification of a tablet, without resorting to the addition of colourants, has led to the introduction of tablets with shapes that are more complex than a simple right circular cylinder (37). The general appearance of any tablet is a relevant factor to consider in patient's compliance and acceptance since, according to the literature, the tablet's shape is usually chosen considering aesthetics and marketing over technical aspects (38). Its visual identity and elegance include many characteristics such as size, shape, colour, odour if applied, taste, consistency and texture of the surface and presence of physical flaws (4). The irregularities in the tablets are mainly caused by the powder sticking to the punches during compression. According to other authors, this phenomenon is related to the roughness of the punches surface and the blend composition. The roughness of the punches tip is thought to increase the adhesion of the powder and therefore leading to an increased number of imperfections (39). Also, as cited in another article, the powder adhesion to the upper punch face during compaction has shown to be reduced when the punch tip curvature is increased. Increasing punch curvature increases the amount of material enclosed within the punch tip during compression, which is relatively protected until the main body of the compact is compressed to low porosity and acts as a secondary punch face to compact the protected material (40). The punches used in this study were brand new and revealed a good quality smooth surface with no visible imperfections and relative curvature, leading to minimal powder adherence. Regarding the positive results, we can confirm that the blend composition had an appropriate fraction of lubricant. Consequently, the produced tablets presented a cloverleaf shape with a regular cross line (Figure 3) and an overall good appearance, with no signs of capping or lamination reported in previous studies (41). This novel shape is an essential characteristic that can be used as an exclusive feature, which is useful for a faster unmistaken identification thus leading to an improvement in compliance. The obtained tablets presented a white colour, which according to previous studies is the preferred colour, contributing to appropriate appearance and acceptable organoleptic properties of the tablets (7).

Table 2 Tablet characterisation results for batches 1-12

Batch	Height (mm)	Diameter (mm)	Weight		Mass of the subdivided tablet		Content Uniformity (CV%)		Weight Loss (%)	Resistance to Crushing (N)	Friability (%)	Wetting Time (min)	Water Absorption Ratio (%)	Disintegration Time (min)
			Mean (mg)	CV%	Mean (mg)	CV%	Mean Content (mg)	CV%						
1	3.984	12.037	401.75	0.82	100.35	5.43	14.016	1.04	0.31	92	0.58	1.85	36.39	3.24
2	3.819	12.033	391.43	0.24	97.73	5.42	13.454	3.65	0.22	103	0.28	3.14	26.10	4.24
3	3.800	12.029	397.67	0.79	99.32	6.38	14.562	1.90	0.26	134	0.19	3.56	35.40	5.47
4	4.561	12.037	489.60	0.50	122.46	7.36	16.376	0.33	0.31	120	0.48	2.19	25.39	4.42
5	4.556	12.043	495.44	0.57	123.69	6.87	18.799	7.53	0.29	151	0.36	3.04	20.90	5.80
6	4.549	12.037	501.26	0.37	124.99	5.06	18.033	1.78	0.24	205	0.27	3.11	26.22	6.71
7	3.998	12.050	398.25	0.92	99.96	5.09	14.296	0.74	0.32	67	0.30	2.13	45.79	3.67
8	3.808	12.032	389.97	0.89	98.12	5.80	14.546	1.94	0.18	100	0.29	2.98	21.51	4.89
9	3.798	12.033	396.53	1.33	99.18	5.40	14.623	0.68	0.25	122	0.18	4.27	37.74	5.49
10	4.675	12.048	495.00	0.83	123.61	5.06	17.245	1.06	0.21	99	0.52	2.43	32.92	5.00
11	4.565	12.073	503.23	1.16	125.45	5.22	20.024	8.08	0.25	170	0.36	2.98	26.63	6.36
12	4.550	12.041	501.97	0.65	124.98	5.81	20.249	7.44	0.36	174	0.28	4.80	27.57	6.97

4.1.2 Thickness and Diameter

As shown in previous studies, scored tablets should be at least 8 mm of diameter to be well managed and the thinner they are, the easier to break. Nevertheless, the diameter as to be taken into consideration because even the thinnest tablet if small in diameter can be more difficult to handle, especially for the older patients (23).

In the punch and die manufacturer's design, made according to the results analysed in previous studies, the diameter of the tablet is 12 mm (Figure 3) which is consistent with the diameter results obtained for all the batches. The coefficient of variation obtained with the average diameters from all trials was minimal 0.098%, meaning this that the altering variables (compression pressure, weight and speed) didn't influence the results and the only significant parameter was the dimension and shape of punch and dial. This is expected when the powder in the dial suffers a plastic deformation caused by the increase of the axial pressure when a radial force is applied (42).

Contrarily to diameter's results, the thickness of the tablets was influenced by the changes made in the amount of powder bed in the die and the compression force. Analysing the results, the trials 1, 2, 3, 7, 8, 9, that aimed for tablets with 400 mg, revealed values around 3.8 mm of height and trials 4, 5, 6, 10, 11, 12, that aimed for tablets with 500 mg, showed values around 4.5 mm. These results suggest that the higher the amount of powder supplied, the heavier and thicker the tablet is. Another relation is seen, (e.g. trials 1, 2, 3) between the compression force of the upper punch and the height of the tablets. A decrease in tablet thickness was observed with the increase of the compression pressure, leading to a denser tablet. This result can be explained by the particle rearrangement and consequent displacement of gas in the powder bed, hence leading to a volume reduction (42).

The results observed, for both parameters (diameter and thickness), from each batch showed low variability, thus supporting the reproducibility of the formulation and tableting process used in this study (43).

4.1.3 Uniformity of mass

The weight uniformity of tablets is expected to be according to the European Pharmacopoeia guidelines where there should be no more than two individual masses with a percentage of more than 5% deviation of the mean value, and none deviating more than 10%. This section also specifies that the acceptable percentage deviation

limit for tablets with more than 250 mg, which is related to the case of study, is 5% (8). All batches complied with this requirement, hence showing a minimal variation from the mean weight, where the mean deviation of all batches was less than 1%. Suggesting this that between batches and, also in the same batch, the tablets produced were all identical in weight, supporting the reproducibility of the formulation and tabletting process. This fact, also corroborated by literature, can be explained by the good flowability properties shown by the excipients overall, particularly the co-processed one, used in the direct compression (15,43). The main reason for this phenomenon is the impregnation of one particle into the matrix of another, hence reducing the rough particle surfaces and forming a near-optimal size distribution, causing better flow properties (26). The angle of repose, commonly used to evaluate the flow of a powder, if under 30^{o} suggests free-flowing material properties and between 31^{o}-35^{o} good flow potential. Also, indices such as Hausner ratio and Carr's Index are used to measure powder's flowability. For a free-flowing powder, the Hausner ratio includes values until 1.2 and for the Carr's Index values situated between 1% and 15% (8,14,44–46). As evaluated in a previous article, the co-processed excipient Prosolv ODT G2®, revealed an angle of repose of 30.96^{o}, a Hausner ratio of 1.21 and Carr's Index of 17.20%, values relatively close to the free-flowing properties, hence showing overall good flowability characteristics (47). Even though the API used was furosemide, which is an extremely electrostatic powder and could cause an uneven mix, the final mixture obtained was satisfying regarding flowability features, leading to a uniform die fill during the direct compression (45).

Analysing the results where the speed rotation was changed another result can be seen. Observing the trials where the rotation speed used in the direct compression was lower (batches 1, 2, 3, 4, 5, 6), the results revealed an inferior percentage of deviation from the mean weight when compared with the ones where a higher rotation speed was used (batches 7, 8, 9, 10, 11, 12). As a similar result to the ones seen in the literature, this can be justified by the fact that when a higher rotation speed is used the powder of the mixture doesn't have enough time to fall and fill completely the dial hence creating variations in the amount of powder in each die and subsequently producing differences in the weights and densities of the tablets (42).

The results, where the production conditions (weight, mechanical strength and speed rotation) were changed, showed some consistent results when compared with each other. For instance, the batches 1, 2, 3, 7, 8, 9 were produced with the aim of 400 mg for each tablet, and so the means of the weight stood close to this value and to each other. The same was observed for batches 4, 5, 6, 10, 11, 12 where the aim was 500 mg. This confirms that when we aim for a specific weight although the

compression force and the rotation speed are changed (trials 1, 2, 3), the results stand close to the established value. Meaning this that the amount of powder supplied and weight set for the machine is the most relevant factor when explaining the weight results.

4.1.4 Uniformity of mass of the subdivided tablet

To evaluate the efficacy and performance of the score marks in the breaking process, one of the tests that must be assessed is the uniformity of mass of the subdivided parts (19). This process is done during the development of the product and to comply with the test, according to the Monographs on dosage forms of the European Pharmacopoeia, no more than one individual mass can be outside the limits of 85% to 115% of the average mass. The tablets also fail to comply with the test if one individual mass is outside the limits of 75% to 125% of the average mass (8).

The results from all batches were according to the expectations of the test, hence showing low mass deviations between pieces of tablets from the same batch. The maximum deviation from the mean value was on trial 4 with a CV% of 7.36%, all the others presented deviations around 5%, indicating their equal breaking. This result is very promising if compared with the ones found in literature where in 60% of the investigated tablets the majority of subdivided tablet weights deviated by more than 10% from the theoretical weight. Or if compared with a study made with twelve commercial angiotensin-converting-enzyme-inhibitors where the relative standard deviation of the masses of the manually subdivided parts ranged from 2.1 up to 23.2%. In this last test, almost all the tablets would be rejected if the test for uniformity of mass of single-dose preparations of the European Pharmacopoeia was applied to the broken tablets and only about 50% of the investigated tablets would meet the test proposed by the investigators (19).

Taking the obtained results into consideration, we can affirm that the cloverleaf shape, size, deepness of the score line, curvature and thickness of the tablet, in this case, revealed outstanding results in the uniformity of mass in the subdivided tablets.

4.1.5 Uniformity of content

To ensure the effectiveness of the subdivision provided by break-marks, a uniformity of content of each dosage unit must be assessed, to guarantee that the

patient will receive the intended dose. The test for uniformity of content is based on the assay of individual content of drug substance(s) in a number of individual dosage unit to determine whether the individual content is within the limits. According to the Monographs on dosage forms of the European Pharmacopoeia the content of each individual unit should be within 85-115% of the overall unit's content, and the batch passes if all tablet units fall within this range. Failure to pass occurs when more than one tablet unit falls outside such limits, or if it falls outside of the range 75-125 % (8,48).

Looking at the formulation of the tablets in this study, the substance of analysis in this test is the furosemide which represents 15% of the whole tablet. Therefore, if the powder was obtained by a homogeneous mixture, it would be expected that each unit of the cloverleaf tablet also contained 15% of API. The results of all batches presented tablet units with very acceptable mean percentages of furosemide rounding 15%, ensuring that the intended dose would be given. In Table 2 the uniformity of each unit among a specific batch is expressed in terms of coefficient of variation percentage, this allows to determine the deviation of content between units and from the mean result. All batches complied with the requirements of the European Pharmacopoeia for uniformity of content. All the values for the furosemide content per unit were inside the limits, and the obtained CV% results were very low, being the higher values in batches 5, 11, 12. This results also showed excellent results if compared with other articles where six anticoagulants were studied, and no tablet quarters would pass the European Pharmacopoeia test for uniformity of content (19).

Another requirement passed by the tablets in our study is presented in USP's furosemide tablet monograph, where it is recommended that not less than 80% of the labelled amount is dissolved in 60 min. The tablets in our study dissolved completely in less than 30 min (49).

4.1.6 Weight Loss

Besides the difficulty of breaking a tablet and it's subdivision in unequal parts another problem that can be reported is the loss of mass after breaking, due to powdering and fragmentation. Loss of mass can lead to loss of dosage, contamination and health hazards for patients and others (19). This test reflects the viability and accuracy of the tablet's score lines upon breaking by quantifying the amount of powder lost during the process. Tablets from all trials complied with the adapted FDA test for loss of mass with a maximum of 3% (48,50). The mean percent of loss mass of each batch was very low, being 0.36% on batch 12 the highest value, which was a very

satisfying outcome. Our results also stand out if compared with other studies where weight losses up to 27% were reported when breaking tablets into quarters (19). Taking in consideration the formulation of work, the results in the present study are also according to a previous article. As expected the tablets prepared with microcrystalline cellulose, presented significant lower weight loss upon splitting when compared with the tablets prepared with other disintegrating excipients (51).

Comparing the values where the production conditions were changed, no correlation or any pattern associated to their variation was found relevant.

In conclusion, this novel tablet form with all its characteristics not only didn't pose any problems when confronted with this test but revealed outstanding results.

4.1.7 Resistance to crushing

Among the parameters that evaluate the performance of the score lines is the ease of subdivision. This criterion, according to previous studies for scored round tablets has critical factors, which in decreasing order of importance are: resistance to crushing, diameter, score mark, and shape (flat or biconvex). To mimic the force necessary in the tablet's subdivision, resistance to crushing was assessed. Given that the European Pharmacopoeia does not govern the required levels for crushing ODTs, the limits of desirability set were based on the application of a reliable model for predicting the ease of subdivision in conventional tablets, equation 5, stated in a previous review.

$$Ease\ of\ subdivision = expit[-1.56 - \big(0{,}05 \times resistance\ to\ crushing(N)\big) + \big(1.04 \times diameter(mm)\big) + \big(5.16 \times score\ mark(one - sided = 0; two - sided = 1)\big) - \big(0.82 \times thickness(mm)\big) - \big(0{,}90 \times shape(biconvex = 0; flat = 1)\big)]^2 \quad (5)$$

According to this article, the cut-off value for an acceptable ease of subdivision was 0.8, this value was obtained through an *in vivo* test with an elderly population from both genders (20). Analysing our results for crushing resistance, we concluded that all batches presented high values. One explanation for this, also reported formerly, could be the moisture absorption effect of the hygroscopic colloidal silicon dioxide that led to harder tablets (30,52). Moreover, all batches with 400 mg tablets complied with the request of the model, and the batches 5, 6, 11, 12, with 500 mg where higher compression forces were applied, weren't according to the values set for ease of breaking. The crushing resistance results for the indicated 500 mg batches were

superior to the expected, mainly because elevated compression forces applied to a higher amount of powder, lead to an excessive bonding between the API and the co-processed excipient (with good binding properties). This phenomenon of densification occurs when we increase the amount of powder supplied and the compression force. Looking at batches 7 *vs* 10, 8 *vs* 11 and 9 *vs* 12, where the compression force and rotation speed were maintained constant, with the increase in the amount of powder supplied there is also an increase in the crushing resistance. Comparing batches 1, 2, 3, where the amount of powder and velocity of speed were maintained constant, we see that an increase in the compression forces increases the crushing resistance. This results were previously explained in a published article, which stated that higher upper punch forces favoured interparticle bonding and reduced the intermolecular voids, thus increasing the mechanical strength of the tablet (43).

Another factor that influences the mechanical integrity of the tablets is the speed velocity of the tabletting machine (53). As could be seen in batches 1 *vs* 7, 2 *vs* 8 and 3 *vs* 9, where the pressure force and the amount of powder supplied were constant, tablets produced at lower rotation speed presented more resistance to crushing than the ones produced with higher rotations *per* minute. This results, also seen in previous articles (54), can be justified by the time during which the tablets are exposed to the compression force applied. With a higher rotation speed, the particles are subjected to the compression force for less time, leading to tablets with lower mechanical strength, and *vice versa*.

Although the limits for crushing resistance, defined by the article, are plausible for conventional tablets, they are not entirely applicable for orodispersible tablets, since the last ones must be substantially lower in order to disintegrate quickly in the oral cavity (11).

As long as the disintegration time is adequate for ODT's, and the value for ease of subdivision is acceptable, even if determined for conventional tablets, there are no objections to the orodispersible and subdivision parameters.

4.1.8 Friability

The friability test is expected to be according to the European Pharmacopoeia guidelines where a maximum loss of mass, obtained from a single test or the mean of 3 tests, not greater than 1% is considered acceptable for most products (8). All batches complied with this requirement, hence showing very low friability results, with a mean value of 0.34%, where the majority stayed below 0.5% with the exception of batch 1

and 10. Analysing the results when rotation speed and weight were maintained constant (e.g. trials 1, 2, 3), an increase in the compression force, is translated in a decrease of the friability, due to the increase in mechanical strength impacted on the tablets. This decrease, also described in a previous article, can be explained by the stronger solid bondings between the tablet's constituents, leading to denser tablets with more resistance to mechanical abrasion and crush (42). Therefore the closest to an ideal ODT is seen in batch 1, where an increase in friability (respecting the limits of 1%) is related to a decrease in the crushing resistance. This batch due to its porosity is expected to have lower times of disintegration and wetting time.

At last, great efforts have been used in order to achieve a compromise between the mechanical strength, enough to endure chipping, abrasion or breaking under conditions of storage, transformation or handling, and the disintegration time, low enough to comply with the requirements of a fast disintegrating tablet (35).

Results show that tablet friability can be affected by the composition of the formulation (e.g., filler, binder, and lubricant) but also by the tablet's shape. In previous studies, the tablet friability resulting from formulation variations was studied under controlled granulation moisture content and tablet crushing resistance. Tablets made with lactose were more friable than tablets made with microcrystalline cellulose. Also, a replacement of 0.5% magnesium stearate with 0.5% stearic acid in the formula reduced tablet friability (55). This suggests that the use microcrystalline cellulose in our formulation is adequate but that magnesium stearate could be replaced by another lubricant with better properties. The tablet punch tip geometry also has shown some influence on tablet friability, depending on the concavity depth. As shown in previous articles tablets compressed with deep concave punches resulted in lower friability, which corroborates the use of the cloverleaf-shaped punches used in our study (55).

4.1.9 Wetting time

Wetting time is believed to be the indicator of the tablet's inner structure and to excipients hydrophilicity. Thus, wetting time of a dosage form is related with the contact angle and was determined to get idea of wetting lag time before disintegration in buccal cavity. The lower the wetting time the quicker is the disintegration of the tablets. Therefore, ODTs require low wetting times, as rapid water imbibition is needed to initiate disintegration (1,2,56).

The results as expected and in resemblance to the water absorption and disintegration test were higher than desirable. Also accordingly with disintegration and friability test the batch 1 presented the best result, taking 1.85 min to be fully imbibed in water, followed by batch 7 with a wetting lag time of 2.13 min. Analysing all batches, the wetting time increases with an increase in compression force, resultant from the reduction in tablet's porosity.

In other studies where the wetting time was evaluated it was observed that, just like in disintegration tests, the type and amount of disintegrant plays an important role. It was revealed that there was a reduction in the wetting time, with both the increase in concentration and combination of superdisintegrants (11). If the chosen combination of disintegrants acts by associating swelling and wicking through capillary mechanisms (e.g. SSG and CCS or Crospovidone) then it leads to a better wetting time comparing with Prosolv ODT® (11,15,57).

4.1.10 Water absorption ratio

The water absorption ratio represents the amount of water that the tablet can absorb and hold. For and ODT a high water absorption ratio is always required because there is limited water in the oral cavity for the disintegration to take place (24). Therefore, the desired value for this test stands above 50%, and none of the batches produced complied with it. The batch 7 that came close to this value with a percentage of 45.79 of water absorbed. Batches produced with lower compression forces and lower weights showed higher water absorption ratios. This can be explained by the lower mechanical strength and free volume within the tablet that allows a greater degree of water imbibition.

Other articles, where this parameter was evaluated, showed that the ideal behind fast disintegration times is the combined effects of swelling ability and high water absorption ratios. Here, the conclusions collide with the previous test where the superdisintegrants and their mechanisms of action are the changing factor to take in consideration (15,35).

4.1.11 Disintegration

This test is provided to determine if the tablets can disintegrate when placed in a water medium under agitation within the prescribed time, which according to the

Section 2.9.1 of the European Pharmacopoeia is 3 min (8). It is interesting to note, though, that the FDA, in a Guidance for Industry paper, requires that the same ODT should disintegrate within 30 seconds, emphasising the idea that fast disintegration is extremely desirable (50). It's not an accurate test since the water transparency is affected by the disintegration of the tablet, becoming turbid, thus making harder to determine the end of the test. Also, the pharmacopoeial test for disintegration doesn't simulate the real *in vivo* conditions (medium volume, temperature and type of forces acting) as it is designed for conventional tablets. So, there is no adequate *in vitro–in vivo* correlation of the results. For this purpose novel methods should be adopted and performed, at body temperature, with salivary fluid and imitation of the tongue acting on the tablet, that better reflect the conditions in the oral cavity (3,58,59).

In this case of study, all the disintegration times failed to comply with the European Pharmacopoeia standards, presenting higher results than the required. These high values were expected, giving the elevated crushing resistance and friability results seen previously, that showed tablets with high mechanical strength, now confirmed not suitable as ODTs (35).

The best result was 3.24 min, which was according to the expectations assumed in the friability test for batch 1. Although this outcome was anticipated, this production process still needs to pass through a process of re-evaluation where some parameters should be changed or adjusted. This reassessment should consider alterations in the type and/or amount of super disintegrant and lubricant in the formulation and the compression forces applied (3). Analysing the first option, previous studies concluded that comparing the Prosolv ODT® with a combination of disintegrants (SSG, CCS and MCC), the combination proved to be more effective in the disintegration time reduction. This fact was explained by the disintegrant additive/synergistic mechanisms of wicking, through capillary action and consequent interparticulate bonds rupture, and swelling that led to quick water uptake causing the tablet to break apart. Considering this, the combination of new super disintegrants (e.g. CCS, SSG, L-HPC) in the right ratio or other co-processed excipients (e.g. F-Melt) could be a plausible alternative to this co-processed excipient (15,24,31,35,56,60). The magnesium stearate, chosen as lubricant, can also be substituted by sodium stearyl fumarate that as shown faster disintegration times in previous articles (24). The second option related to the decrease of the compression of forces should also be tested. This way we could evaluate the viability of tablets produced with lower forces and if they comply with the requirements for the tensile strength, friability and disintegration time tests.

Besides the elevated disintegrations times, the results show that at constant weight and speed, when the compression force increases so thus the tablet's

disintegration time. This conclusion observed in batches 1, 2, 3, can be explained by the densification of the tablets, and consequent reduction of porosity, making more difficult for the water to penetrate (42,43,53). Considering the previous results an association can be made between the increase in compression force, producing harder and less friable tablets, and prolonged disintegration times, caused by the stronger interparticle bonding. With this analysis in mind, the previous biopharmaceutical tests that also evolved the loss of tablet's integrity when in contact with water were expected to lead to high wetting time, and lower absorption capacity.

Another parameter to consider in this test, also analysed in precedent articles, is the amount of powder that fills the die. As seen comparing batches 1 *vs* 4, 2 *vs* 5 and 3 *vs* 6, at a constant force of compression and speed, a higher intake of powder leads to an increase in the disintegration times. This could be predicted given the larger surface area to volume ratio of smaller tablets, which means that more of the tablet is in contact with the water (61).

Looking at batches 1 *vs* 7, 2 *vs* 8 and 3 *vs* 9, where the amount of powder supplied and the compression forces were maintained constant, we can notice that an increase in the speed rotation of the tabletting machine led to higher disintegration times. This result could be explained by the different internal density distribution that may have happened, caused by the cloverleaf shape and the altered independent variable. Changing the geometry of the punch and die set used will inherently change the direction of the resultant forces causing major changes in the direction of powder movement. Other investigations, focused on showing how inherently changing the geometry of the punch and die set used from a flat to curved geometry may enhance the formation of high-density gradients in the tablets and cause eventual failure of the tablets by ‘‘capping’’ or ‘‘lamination’’ (37). Other studies that involved the alteration of the punch geometry concluded that it can lead to large density gradients within the compact. The results for curved-face tablets showed higher density regions in the corners where the powder was in contact with the die wall (41). Also, the increasing punch curvature was found to increase the mechanical strength of the periphery relative to the centre of tablets, which may be related to the case study geometry (40). Previous articles that studied the density distribution among tablets concluded that those with score lines tend to present high-density regions around the edges and low-density regions near the flanks of the breaking lines (62). This fact was attested by the visual observation of our tablet's disintegration process. During the first min the tablets broke into four pieces, following the score line and then the small parts started to disintegrate individually. According to the studies, high-density regions were associated with higher strength and required longer times to disintegrate, increasing

the overall time. When the speed rotation is increased to 20 rpm, the compression force is applied for less time and may lead to uneven densities in the produced tablets. Although these differences in the internal density distribution may be relevant in this test, they didn't seem to have an impact in the crushing resistance and friability tests because the latter two depended strongly on the average density. To assess the density distribution accurately and predict its effects, other tests should be used, for example, X-ray computed tomography (CT), nuclear magnetic resonance imaging (NMRI) or acoustic wave velocity (62,63).

4.2 Analysis of the linear regression results

4.2.1 Mathematical modelling of experimental data

This study aimed to evaluate how the three independent process variables (UF, W, S) interacted and influenced the properties of the produced ODTs. The statistical analysis, given by STATISTICA 7, was assembled (Table 3 and Table 4) showing constants and regression coefficients and correspondent p values for each response. Only statistically significant coefficients ($p < 0.05$) were retained in the equations to increase the R^2 adjusted value. The lack-of-fit test ($p > 0.05$) and the square of the correlation coefficients ($R^2 \approx 1$) indicated when the models were fitted sufficiently to the measured data.

A multiple linear regression method was used to analyse the obtained results from the experimental data, and the following polynomial equation 6, was used:

$$Y = b_0 + b_1x_1 + b_{11}x_1^2 + b_2x_2 + b_3x_3 + b_{12}x_1x_2 + b_{13}x_1x_3 + b_{23}x_2x_3 \quad (6)$$

Where Y is the response and x_1, x_2 and x_3 are the levels of the independent variables. 1, 2 and 3 denote the independent variables: upper punch force, tablet weight and speed respectively. Where b_0 represents the intercept, b_1 is the coefficient of the linear effect of independent variable 1, b_{11} is the coefficient of the quadratic effect of variable 1 and b_{12} is the coefficient of the interaction between variables 1 and 2. The notations 'L' and 'Q' represent the linear and quadratic functions of each independent variable, while '1L by 2L' represents the interaction between the linear responses of the independent variables 1 and 2 (35,43,64).

Table 3 Statistical analysis for batches 1-12, showing the response coefficient (Coef) for each variable and their corresponding p values (p), along with the correlation coefficient (R^2 and R^2 Adjusted).

	Thickness		**Uniformity of Mass**		**Content Uniformity**		**Weight Loss**		**Resistance to Crushing**		**Friability**	
	Coef	p	Coef	p	Coef	p	Coef	p	Coef	p	Coef	p
Intercept	4.222	0.000	0.756	0.000	3.013	0.001	0.267	0.000	128.825	0.000	0.340	0.000
UF L	-0.065	0.005*			1.077	0.129			32.238	0.000*	-0.120	0.001*
UF Q	-0.026	0.060			1.714	0.018*						
W L	0.354	0.000*	-0.076	0.290	1.356	0.035*			25.725	0.001*	0.037	0.083
S L	0.010	0.334	0.208	0.015*					-5.242	0.257	-0.019	0.332
1L by 2L	0.031	0.057	-0.086	0.323	0.879	0.201	0.025	0.168	7.938	0.171		
1L by 3L	-0.016	0.237					0.025	0.168			0.028	0.247
2L by 3L	0.010	0.341			0.847	0.141					0.028	0.166
R^2	0.997		0.600		0.812		0.333		0.812		0.872	
R^2 Adjusted	0.992		0.450		0.655		0.184		0.655		0.765	

Only statistically significant coefficients ($p < 0.05$) were assembled and marked with (*)

Table 4 Statistical analysis for batches 1-12, showing the response coefficient (Coef) for each variable and their corresponding p values (p), along with the correlation coefficient (R^2 and R^2 Adjusted).

	Wetting Time		Water Absorption Ratio		Disintegration Time	
	Coef	p	Coef	p	Coef	p
Intercept	3.040	0.000	30.212	0.000	5.188	0.000
UF L	0.893	0.000*	-1.694	0.328	1.039	0.000*
UF Q			-4.821	0.013*	0.101	0.051
W L			-3.608	0.032*	0.688	0.000*
S L	0.225	0.041*	1.812	0.213	0.208	0.002*
1L by 2L						
1L by 3L	0.235	0.072	-1.656	0.338	-0.091	0.105
2L by 3L						
R^2	0.901		0.801		0.993	
R^2 Adjusted	0.863		0.635		0.987	

Only statistically significant coefficients ($p < 0.05$) were assembled and marked with (*)

4.2.2 Thickness

The upper compression force demonstrated a linear effect (UF L) on the height of tablets with a negative coefficient. This points towards a decrease in height with an increase in the upper compression force, thus leading to an increase in the tablet's density (43). The weight of the tablets also displayed a linear effect (W L) on the height of tablets this time with a positive coefficient, meaning that as the weight of tablets increased, so did the tablet's height. According to the previous conclusion in this study, both linear effects were expected, given that as we increased the compression force, the free volume of the powder mix was reduced, hence reducing the thickness. When the weight of tablet increased, a higher quantity of powder was used and so the tablets were inevitably higher, since the diameter is a constant value of the punches and dial. Concerning the adjusted R^2, its high value for this response indicates a high degree of the model's accuracy regarding the experimental and predicted response. An adjusted R^2 of 0.992 for height indicates that over 99.20% of the variation in the response is taken into consideration in the regression equation.

4.2.3 Uniformity of mass

The results show that the effects of the upper force and the weight of tablets were not statistically significant in this case, though the speed of the tablet die showed a linear effect on the uniformity of weight. Given the positive coefficient of speed (S L), there is an increase in the weight CV% when the speed of rotation increases. It can be observed that the multiple correlation coefficient (R^2) is reasonably low for this response, indicating that there is a low degree of correlation between the experimental and predicted responses. The adjusted R^2 of 0.450 for weight CV% indicates that over 45% of the variation in the response is accounted for in the regression equation.

4.2.4 Uniformity of content

The analysis shows a positive coefficient on the content uniformity for both the quadratic upper compression force (UF Q) and linear weight (W L) effect. The positive quadratic effect shows that as the upper force increases, the CV% decreases to a minimum value, after which increases.

The turning point that is represented by the minimum value of the parabolic curve is calculated using the equation 7:

$$x = -\frac{b}{2a} \quad (7)$$

Where x represents the minimum or maximum value of the parabolic curve, b represents the quadratic coefficient, and a denotes the linear coefficient.

According to the model described the turning point in the uniformity of content happens when the upper compression force reaches 11.35 kN. This result once again supports the use of lower compression forces, previously suggested as an alternative for manufacturing improvement.

The linear weight effect is described by the increase in the CV% with the increase of the amount of powder supplied.

The correlation coefficient (Adjusted R^2 = 0.655) is significant meaning that the proposed model fits the responses.

4.2.5 Weight Loss

The variables changed in this study didn't present relevant statistical results regarding the weight loss ($p > 0.05$) and obtained very low correlation coefficients (Adjusted R^2 = 0.184).

4.2.6 Resistance to Crushing

The statistical results for crushing resistance show a very large correlation coefficient for both upper force and weight linear effect (UF L and W L). Meaning this that as the compression force increases, there is an increase in the mechanical strength and in the force needed to crush the tablet, as seen before in this study. High compression force reduces the intermolecular voids resulting in densification due to greater interparticle bonding. Both enhanced binding and densification result in increased tablet tensile strength and resistance to crushing (43). Regarding the weight we also see the same pattern as it increases, also does the necessary force to crush the tablet.

The high correlation coefficient (Adjusted R^2 = 0.872) denotes that the mathematical model used is adequate to the produced responses.

4.2.7 Friability

The statistical analysis revealed a negative coefficient for the linear effect of the upper punch force. Meaning this that as the compression force increases, the friability decreases. This, as explained in the previous chapter, is due to the particle bonding and consequent increase in the mechanical strength of the tablets when higher compression is used. The respective correlation coefficient is shown to have reasonably high values (Adjusted $R^2 = 0.765$).

4.2.8 Wetting time

The statistical results show positive coefficients for the linear effect of the upper punch force and the rotation speed. Meaning that an increase in this variables is accountable for the increase in the wetting time of the tablets. This is again explained by the decrease in the porosity when higher compression forces are utilised and the different densities within the tablet structure. This densification with different distributions makes harder for the water to penetrate into the tablets, leading to prolonged wetting times. Once again the correlation coefficient showed a high value, demonstrating that over 86.3% of the variation in the response is taken into consideration in the regression equation.

4.2.9 Water absorption ratio

The statistical results for the water absorption ratio revealed negative coefficients for both the quadratic effect of the upper force (UF Q) and the linear effect of the weight (W L). The negative quadratic effect shows that as the upper force increases, the water absorption ratio increases to a maximum, after which it decreases. The turning point, calculated based on equation 7, was 9.66 kN, maximum after which the ratio of water absorption decreased. Since we are working with a multiple linear regression, that includes both experimental data and predicted values for the independent variables, it is expected the presence of values outside the selected experimental range. The value 9.66 kN is an example of a result that is out of the experimental range but predicts the optimum force to obtain the best water absorption ratio. Meaning this that an increase in the compression force beyond 9.66 kN, which includes all the experimental chosen values, leads to a decrease in water absorption ratio. This specific value, alongside with other results from the disintegration and wetting time tests, give an indication that

a decrease in the compression forces used should be assessed in order to obtain better results. The negative linear effect of the weight demonstrates that the higher the tablet's weight, the lower the water absorption ratio. These results were explained in previous tests, where the higher the weight and forces applied the more compact and harder the structure of the tablet, making harder for water to penetrate. The obtained correlation coefficient (Adjusted R^2 = 0.635) was significant, demonstrating the mathematical model's ability to fit in the produced responses.

4.2.10 Disintegration

The linear effects of the upper punch force, tablet weight and speed revealed significance in the production of scored ODTs, and statistical analysis showed a positive coefficient for all of them. This result indicates that every time each one of the independent variables increases so does the disintegration time. As seen before, both the increase in compression force and weight led to harder and denser tablets with reduced porosity, making harder for the water to penetrate. Also as previously analysed, the different density distributions have shown to increase the overall disintegration time. Taking this facts into consideration the linear effects for the three independent variables were all expected outcomes. The obtained correlation coefficient was very high demonstrating the suitability of the proposed mathematical model (Adjusted R^2 = 0.987).

4.3 Classic EBT punches *vs* Novel EBT punches design

The tablets produced in this study presented a novel shape (Figure 3), given by new EBT punches, designed and produced specifically for this matter of investigation. Besides their obvious appealing cloverleaf shape, when compared with a previous study in the same conditions (equal formulation and independent variables studied) but with classic EBT shape (Figure 4), they also presented interesting results. The results of the tablets with novel shape showed better weight and content uniformity, less percentage of weight loss during the subdivision of the tablet and lower friability results. The crushing resistance results presented very high values hence suggesting that lower compression forces could be employed, with a gain both in the ease of breaking and the energetic consume in the manufacturing process. One consequence

of this high mechanical strength of the tablets was demonstrated in the prolonged disintegration and wetting times and lower water absorption ratios. The biopharmaceutical tests in the cloverleaf-shaped tablets revealed worse results than the ones obtained with the classic EBT punches but showed space for improvement. These results suggest that some changes should be made in the production process but, the novel EBT punch design is a valuable asset and worthy investment with the ability to stand as a game changer in the ODT market (65).

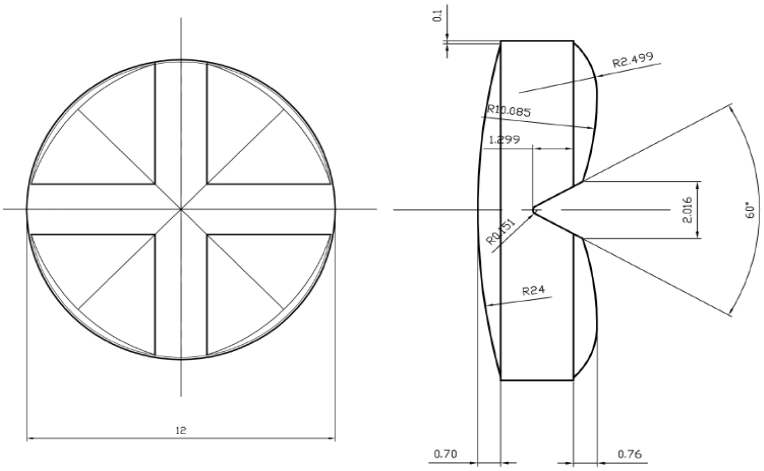

Figure 4 Diagrammatic representation of orally dispersible tablets produced using "Easy Breakable Tablet" punch classic design

5 Conclusions

In this study, scored orodispersible tablets were manufactured and changes were made during the production process in the compression force, tablet weight and speed rotation of the tabletting machine. This variations led to differences in the tablets properties that were evaluated through DoE. The tablets presented a cloverleaf shape with regular score lines, a novel characteristic that can be used as an exclusive feature and can lead to an improvement in patient's compliance and acceptance.

Besides the variations made, the obtained ODTs were according to the limits set by the European Pharmacopoeia for both weight and content uniformity, showing that the die fill was adequate and the formulation presented good flowability properties. All batches revealed tablet units with very low coefficients of variation and satisfactory mean percentages of furosemide rounding 15%, ensuring that the intended dose is given. To evaluate the efficacy and performance of the score mark, tests like breaking ease, uniformity of the subdivided tablets and loss of mass by the subdivision were assessed. The breaking ease was determined analysing the resistance to crushing, which revealed very high values as a result of denser tablets with excessive bonding and mechanical strength. This fact was also corroborated by the very low friability results presented by the tablets when facing mechanical abrasion. The results also showed uniformity of the subdivided tablets with very low mass deviations and minimum percentage of mass lost during breaking process.

The biopharmaceutical tests revealed a different outcome of what was expected from this dosage form. All the disintegration and wetting times failed to comply with the required standards, along with the water absorption ratio. This outcome could be explained by the crushing resistance and friability results, along with possible different internal density distributions.

6 Future Work

The production process needs to pass through a re-evaluation but, is certain that this novel shape is a worthy investment *versus* the classic EBT design. This reassessment should consider alterations in the type and/or amount of super disintegrant and lubricant in the formulation and the compression forces applied. Another solution could pass through the incorporation of methods that evaluate the porosity and the distributions of density in tablets that could be behind the unexpected biopharmaceutical results.

Future work in this study will focus on the application of a desirability method in order to establish the ideal parameters and evaluate the viability of the model and produced tablets. Afterwards, in a final stage of the product development, an *in vivo* disintegration time test should be done alongside with taste evaluation, and mouthfeel to determine the viability of the tablets. This same tests should also be taken after a few months, at different storage temperatures and relative humidity, to evaluate their chemical and physical stability.

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